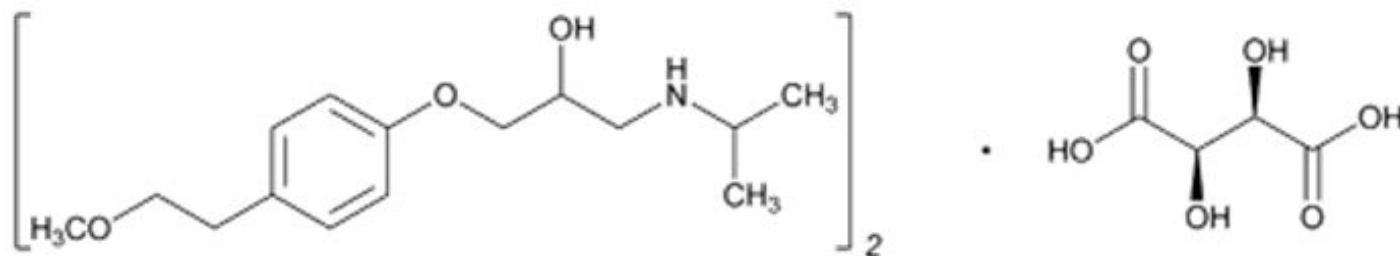


METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE- metoprolol tartrate and hydrochlorothiazide tablet
Mylan Pharmaceuticals Inc.

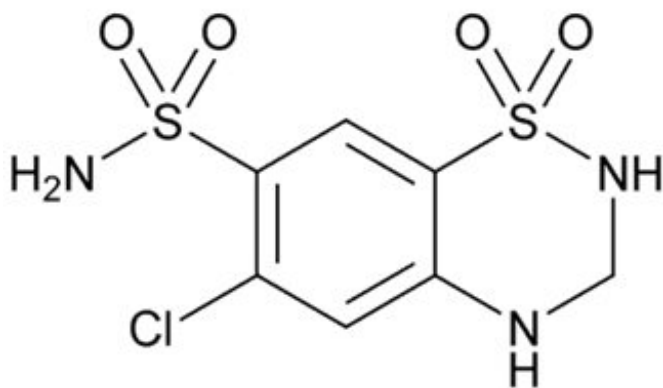
DESCRIPTION

Metoprolol tartrate and hydrochlorothiazide tablets, USP have the antihypertensive effect of metoprolol tartrate, a selective β_1 -adrenoreceptor blocking agent, and the antihypertensive and diuretic actions of hydrochlorothiazide. It is available as tablets for oral administration. The 50 mg/25 mg tablets contain 50 mg of metoprolol tartrate and 25 mg of hydrochlorothiazide; the 100 mg/25 mg tablets contain 100 mg of metoprolol tartrate and 25 mg of hydrochlorothiazide; and the 100 mg/50 mg tablets contain 100 mg of metoprolol tartrate and 50 mg of hydrochlorothiazide. Metoprolol tartrate is (\pm)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt, and its structural formula is:



Metoprolol tartrate, USP is a white, crystalline powder. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether. Its molecular weight is 684.81.

Hydrochlorothiazide is 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, and its structural formula is:



Hydrochlorothiazide, USP is a white, or practically white, practically odorless, crystalline powder. It is freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; slightly soluble in water; and insoluble in ether, in chloroform, and in dilute mineral acids. Its molecular weight is 297.74.

Inactive Ingredients: Anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, FD&C Yellow No. 6 Aluminum Lake, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch (corn) and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

Metoprolol Tartrate

Metoprolol tartrate is a beta-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on beta₁ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol tartrate also inhibits beta₂ adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative beta₁ selectivity has been confirmed by the following: (1) In normal subjects, metoprolol tartrate is unable to reverse the beta₂-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective (beta₁ plus beta₂) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol tartrate reduces FEV₁ and FVC significantly less than a nonselective beta blocker, propranolol at equivalent beta₁-receptor blocking doses.

Metoprolol tartrate has no intrinsic sympathomimetic activity and only weak membrane-stabilizing activity. Metoprolol tartrate crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that metoprolol tartrate slows the sinus rate and decreases AV nodal conduction.

In controlled clinical studies, metoprolol tartrate has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at dosages of 100-450 mg daily. In controlled, comparative, clinical studies, metoprolol tartrate has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, and to be equally effective in supine and standing positions.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Pharmacokinetics

In man, absorption of metoprolol tartrate is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers. Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. The systemic availability and half-life of metoprolol tartrate in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In elderly subjects with clinically normal renal function, there are no significant differences in metoprolol tartrate pharmacokinetics compared to young subjects.

Metoprolol tartrate is extensively metabolized by the cytochrome P450 enzyme system in the liver. The oxidative metabolism of metoprolol tartrate is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the

prevalence of the poor metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% of Asians are poor metabolizers.

Poor CYP2D6 metabolizers exhibit several-fold higher plasma concentrations of metoprolol tartrate than extensive metabolizers with normal CYP2D6 activity. The elimination half-life of metoprolol is about 7.5 hours in poor metabolizers and 2.8 hours in extensive metabolizers. However, the CYP2D6 dependent metabolism of metoprolol tartrate seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol tartrate contribute significantly to its beta-blocking effect.

Pharmacodynamics

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

Hydrochlorothiazide

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage, all thiazides are approximately equal in their diuretic potency. Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

Pharmacokinetics

Hydrochlorothiazide is rapidly absorbed, as indicated by peak plasma concentrations 1-2.5 hours after oral administration. Plasma levels of the drug are proportional to dose; the concentration in whole blood is 1.6-1.8 times higher than in plasma. Thiazides are eliminated rapidly by the kidney. After oral administration of 25- to 100-mg doses, 72-97% of the dose is excreted in the urine, indicating dose-independent absorption. Hydrochlorothiazide is eliminated from plasma in a biphasic fashion with a terminal half-life of 10-17 hours. Plasma protein binding is 67.9%. Plasma clearance is 15.9-30.0 L/hr; volume of distribution is 3.6-7.8 L/kg.

Gastrointestinal absorption of hydrochlorothiazide is enhanced when administered with food. Absorption is decreased in patients with congestive heart failure, and the pharmacokinetics are considerably different in these patients.

Pharmacodynamics

The onset of action of thiazides occurs in 2 hours and the peak effect at about 4 hours. The action persists for approximately 6-12 hours.

INDICATIONS AND USAGE

Metoprolol tartrate and hydrochlorothiazide tablets are indicated for the management of hypertension.

This fixed-combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, therapy with the fixed

combination may be more convenient than with the separate components.

CONTRAINDICATIONS

Metoprolol Tartrate

Metoprolol tartrate is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

Hypersensitivity to metoprolol tartrate and related derivatives, or to any of the excipients; hypersensitivity to other beta blockers (cross sensitivity between beta blockers can occur).

Sick-sinus syndrome.

Severe peripheral arterial circulatory disorders.

Hydrochlorothiazide

Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs (see WARNINGS).

WARNINGS

Metoprolol Tartrate

Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, metoprolol tartrate should be administered cautiously.

In Patients Without a History of Cardiac Failure

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol tartrate should be withdrawn.

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, metoprolol tartrate should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice (see PRECAUTIONS: Information for Patients).

Bronchospastic Diseases

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS, including metoprolol tartrate and hydrochlorothiazide tablets. Because of its relative beta₁ selectivity, however, metoprolol tartrate may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer metoprolol tartrate in smaller

doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (see DOSAGE AND ADMINISTRATION).

Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Metoprolol tartrate should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers, including metoprolol tartrate and hydrochlorothiazide tablets, may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Selective beta blockers do not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, do not delay recovery of blood glucose to normal levels.

Pheochromocytoma

If metoprolol tartrate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) or hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Hydrochlorothiazide

Thiazides should be used with caution in patients with severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

PRECAUTIONS

Patient Information

Non-melanoma Skin Cancer

Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

General

Metoprolol Tartrate

Metoprolol tartrate should be used with caution in patients with impaired hepatic function.

Hydrochlorothiazide

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis, and hypokalemia (see Laboratory Tests and Drug/Drug Interactions). Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance, such as nausea or vomiting.

Hypokalemia may develop, especially in cases of brisk diuresis or severe cirrhosis.

Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia may be avoided or treated by the use of potassium supplements or foods with a high potassium content.

Any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In cases of actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Latent diabetes may become manifest during thiazide administration (see Drug/Drug Interactions).

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, withholding or discontinuing diuretic therapy should be considered.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen.

Thiazide diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Information for Patients

Patients should be advised to take metoprolol tartrate and hydrochlorothiazide tablets regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue metoprolol tartrate and hydrochlorothiazide tablets without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with metoprolol tartrate and hydrochlorothiazide tablets has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking metoprolol tartrate and hydrochlorothiazide tablets.

Laboratory Tests

Metoprolol Tartrate

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Hydrochlorothiazide

Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Drug/Drug Interactions

Metoprolol Tartrate

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol tartrate plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Both digitalis glycosides and beta blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Risk of Anaphylactic Reaction

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

General Anesthetics

Some inhalation anesthetics may enhance the cardiodepressant effect of beta blockers (see **WARNINGS: Metoprolol Tartrate: Major Surgery**).

CYP2D6 Inhibitors

Potent inhibitors of the CYP2D6 enzyme may increase the plasma concentration of metoprolol tartrate. Strong inhibition of CYP2D6 would mimic the pharmacokinetics of CYP2D6 poor metabolizer. Caution should therefore be exercised when administering potent CYP2D6 inhibitors with metoprolol tartrate. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine.

Clonidine

If a patient is treated with clonidine and metoprolol tartrate concurrently, and clonidine treatment is to be discontinued, metoprolol tartrate should be stopped several days before clonidine is withdrawn. Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta blocker treatment.

Hydrochlorothiazide

Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Hypokalemia may develop during concomitant use of steroids or ACTH.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to norepinephrine, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Thiazides may increase the responsiveness to tubocurarine.

Lithium renal clearance is reduced by thiazides, increasing the risk of lithium toxicity.

There have been rare reports in the literature of hemolytic anemia occurring with the concomitant use of hydrochlorothiazide and methyldopa.

Concurrent administration of some nonsteroidal anti-inflammatory agents may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

Cholestyramine and Colestipol Resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Drug/Laboratory Test Interactions

Hydrochlorothiazide

Thiazides may decrease serum levels of protein-bound iodine without signs of thyroid disturbance. Thiazides should be discontinued before tests for parathyroid function are made (see PRECAUTIONS: General: Hydrochlorothiazide: Calcium excretion).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Metoprolol Tartrate and Hydrochlorothiazide Tablets

Carcinogenicity and mutagenicity studies have not been conducted with metoprolol tartrate and hydrochlorothiazide tablets. Metoprolol tartrate and hydrochlorothiazide tablets produced no evidence of impaired fertility in male or female rats administered gavage doses up to 200/50 mg/kg (100/50 times the maximum recommended daily human dose) prior to mating and throughout gestation and rearing of young.

Metoprolol Tartrate

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, or in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at

doses up to 55.5 times the maximum daily human dose of 450 mg.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses up to approximately 600 mg/kg/day) or in male and female rats (at doses up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium* (Ames assay) and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 mg/kg/day and 4 mg/kg/day, respectively, prior to mating and throughout gestation.

Pregnancy

Teratogenic Effects

Metoprolol Tartrate and Hydrochlorothiazide Tablets

No evidence of adverse effects on pregnancy or the fetus were observed in rats when dams were administered gavaged doses up to 200/50 mg/kg of metoprolol tartrate and hydrochlorothiazide tablets (100/50 times the maximum recommended daily human dose) during the period of organogenesis. Increased postimplantation loss and decreased postnatal survival were observed with these doses when administered later in pregnancy (gestation days 15-21). In rabbits, increased fetal loss was observed with oral doses of 25/6.25 mg/kg of metoprolol tartrate and hydrochlorothiazide tablets (12/6 times the maximum recommended daily human dose), but not with lower doses. There are no adequate and well-controlled studies of metoprolol tartrate and hydrochlorothiazide tablets in pregnant women. Metoprolol tartrate and hydrochlorothiazide tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Metoprolol Tartrate

Metoprolol tartrate has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of teratogenicity.

Hydrochlorothiazide

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 mg/kg/day and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

Nonteratogenic Effects

Hydrochlorothiazide

Thiazides cross the placental barrier and appear in cord blood, and there is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers

Metoprolol tartrate is excreted in breast milk in a very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of metoprolol of less than 1 mg. Thiazides are also excreted in breast milk. If the use of metoprolol tartrate and hydrochlorothiazide tablets is deemed essential, the patient should stop nursing.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of metoprolol tartrate and hydrochlorothiazide tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see WARNINGS). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

ADVERSE REACTIONS

Metoprolol Tartrate and Hydrochlorothiazide Tablets

The following adverse reactions were reported in controlled clinical studies of the combination of metoprolol tartrate and hydrochlorothiazide.

Body as a Whole: Fatigue or lethargy and flu syndrome have each been reported in about 10 in 100 patients.

Nervous System: Dizziness or vertigo, drowsiness or somnolence, and headache have each occurred in about 10 in 100 patients. Nightmare has occurred in 1 in 100 patients.

Cardiovascular: Bradycardia has occurred in about 6 in 100 patients. Decreased exercise tolerance and dyspnea have each occurred in about 1 of 100 patients.

Digestive: Diarrhea, digestive disorder, dry mouth, nausea or vomiting, and constipation have each occurred in about 1 in 100 patients.

Metabolic and Nutritional: Hypokalemia has occurred in fewer than 10 in 100 patients. Edema, gout, and anorexia have each occurred in 1 in 100 patients.

Special Senses: Blurred vision, tinnitus, and earache have each been reported in 1 in 100 patients.

Skin: Sweating and purpura have each occurred in 1 in 100 patients.

Urogenital: Impotence has occurred in 1 in 100 patients.

Musculoskeletal: Muscle pain has occurred in 1 in 100 patients.

Metoprolol Tartrate

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported, but a drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; and congestive heart failure have been reported. Gangrene in patients with pre-existing severe peripheral circulatory disorders has also been reported very rarely (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) has been reported in fewer than 1 of 100 patients (see WARNINGS). Rhinitis has also been reported.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100, or fewer, patients. Vomiting was a common occurrence. Postmarketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

Hypersensitive Reactions: Pruritus has occurred in fewer than 1 of 100 patients. Rash has been reported. Very rarely, photosensitivity and worsening of psoriasis has been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Alopecia has been reported. There have been very rare reports of weight gain, arthritis, and retroperitoneal fibrosis (relationship to metoprolol tartrate has not been definitely established).

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with metoprolol tartrate.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol tartrate.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Postmarketing Experience

The following adverse reactions have been reported during postapproval use of metoprolol tartrate: confusional state, an increase in blood triglycerides and a decrease in High Density Lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Non-melanoma Skin Cancer

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall

population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of $\geq 50,000$ mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

Hydrochlorothiazide

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. Consequently, the reactions are categorized by organ systems and are listed in decreasing order of severity and not frequency.

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic), sialadenitis, vomiting, diarrhea, cramping, nausea, gastric irritation, constipation, anorexia.

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

Neurologic: Vertigo, dizziness, transient blurred vision, headache, paresthesia, xanthopsia, weakness, restlessness.

Musculoskeletal: Muscle spasm.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia.

Metabolic: Hyperglycemia, glycosuria, hyperuricemia.

Hypersensitive Reactions: Necrotizing angitis, Stevens-Johnson syndrome, respiratory distress including pneumonitis and pulmonary edema, purpura, urticaria, rash, photosensitivity.

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Acute Toxicity

Several cases of overdose with metoprolol tartrate have been reported, some leading to death. No deaths have been reported with hydrochlorothiazide.

Oral LD₅₀'s (mg/kg): mice, 1158 (metoprolol tartrate); rats, 3090 (metoprolol tartrate), 2750 (hydrochlorothiazide).

Signs and Symptoms

Metoprolol Tartrate

Potential signs and symptoms associated with overdose with metoprolol tartrate are bradycardia, hypotension, bronchospasm, and cardiac failure.

Hydrochlorothiazide

The most prominent feature of poisoning is acute loss of fluid and electrolytes.

Cardiovascular: Tachycardia, hypotension, shock.

Neuromuscular: Weakness, confusion, dizziness, cramps of the calf muscles, paresthesia, fatigue, impairment of consciousness.

Digestive: Nausea, vomiting, thirst.

Renal: Polyuria, oliguria, or anuria (due to hemoconcentration).

Laboratory Findings: Hypokalemia, hyponatremia, hypochloremia, alkalosis; increased BUN (especially in patients with renal insufficiency).

Combined Poisoning: Signs and symptoms may be aggravated or modified by concomitant intake of

antihypertensive medication, barbiturates, curare, digitalis (hypokalemia), corticosteroids, narcotics, or alcohol.

Treatment

There is no specific antidote.

On the basis of the pharmacologic actions of metoprolol tartrate and hydrochlorothiazide, the following general measures should be employed:

Elimination of the Drug

Inducement of vomiting, gastric lavage, and activated charcoal.

Bradycardia

Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension

The patient's legs should be elevated and lost fluid and electrolytes (potassium, sodium) should be replaced. A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm

A beta₂-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure

A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Surveillance

Fluid and electrolyte balance (especially serum potassium) and renal function should be monitored until conditions become normal.

DOSAGE AND ADMINISTRATION

Dosage should be determined by individual titration (see INDICATIONS AND USAGE).

Hydrochlorothiazide is usually given at a dosage of 12.5 to 50 mg per day. The usual initial dosage of metoprolol tartrate is 100 mg daily in single or divided doses. Dosage may be increased gradually until optimum blood pressure control is achieved. The effective dosage range is 100 to 450 mg per day. While once-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period, and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta₁ selectivity diminishes as dosage of metoprolol tartrate is increased.

The following dosage schedule may be used to administer from 100 to 200 mg of metoprolol tartrate per day and from 25 to 50 mg of hydrochlorothiazide per day:

<i>Metoprolol Tartrate and Hydrochlorothiazide Tablets</i>	<i>Dosage</i>
Tablets of 50/25	2 tablets per day in single or divided doses
Tablets of 100/25	1 to 2 tablets per day in single or divided doses

Dosing regimens that exceed 50 mg of hydrochlorothiazide per day are not recommended. When necessary, another antihypertensive agent may be added gradually, beginning with 50% of the usual recommended starting dose to avoid an excessive fall in blood pressure.

HOW SUPPLIED

Metoprolol Tartrate and Hydrochlorothiazide Tablets, USP are available containing 50 mg or 100 mg of metoprolol tartrate, USP and 25 mg or 50 mg of hydrochlorothiazide, USP providing for the following available combinations: 50 mg/25 mg, 100 mg/25 mg or 100 mg/50 mg.

The 50 mg/25 mg tablets are peach, round, scored tablets debossed with **M** above the score and **424** below the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0424-01
bottles of 100 tablets

The 100 mg/25 mg tablets are peach, oval, scored tablets debossed with **M** to the left of the score and **434** to the right of the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0434-01
bottles of 100 tablets

The 100 mg/50 mg tablets are peach, capsule-shaped, scored tablets debossed with **M** to the left of the score and **445** to the right of the score on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-0445-01
bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Revised: 8/2020
MPHCTZ:R5

PRINCIPAL DISPLAY PANEL - 50 mg/25 mg

NDC 0378-0424-01

**Metoprolol
Tartrate and
Hydrochlorothiazide
Tablets, USP
50 mg/
25 mg**

Rx only 100 Tablets

Each tablet contains:
Metoprolol tartrate, USP 50 mg
Hydrochlorothiazide, USP 25 mg

Dispense in a tight, light-resistant

container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

Store at 20° to 25°C (68° to 77°F).

**[See USP Controlled Room
Temperature.]**

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0424A4

Each tablet contains:
Metoprolol tartrate, USP 50 mg
Hydrochlorothiazide, USP 25 mg

NDC 0378-0424-01

**Metoprolol
Tartrate and
Hydrochlorothiazide**
Tablets, USP

**50 mg/
25 mg**

Mylan®

Rx only 100 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]
Protect from moisture.
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
Mylan.com

RM0424A4

GTIN XXXXXXXXXXXXXXXX
S/N XXXXXXXXXXXXXXXX
EXP MM YYYY
LOT XXXXXXXX

PRINCIPAL DISPLAY PANEL - 100 mg/25 mg

NDC 0378-0434-01

**Metoprolol
Tartrate and
Hydrochlorothiazide
Tablets, USP**

**100 mg/
25 mg**

Rx only 100 Tablets

Each tablet contains:

Metoprolol tartrate, USP 100 mg
Hydrochlorothiazide, USP 25 mg

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]**

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0434A4

Each tablet contains:
Metoprolol tartrate, USP 100 mg
Hydrochlorothiazide, USP 25 mg

NDC 0378-0434-01

**Metoprolol
Tartrate and
Hydrochlorothiazide**
Tablets, USP

**100 mg/
25 mg**

Mylan®

Rx only 100 Tablets

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication
out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from moisture.
Usual Dosage: See accompanying
prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan®
Mylan.com

RM0434A4



**PRINCIPAL DISPLAY PANEL - 100 mg/50 mg
NDC 0378-0445-01**

**Metoprolol
Tartrate and
Hydrochlorothiazide
Tablets, USP
100 mg/
50 mg**

Rx only 100 Tablets

Each tablet contains:

Metoprolol tartrate, USP 100 mg

Hydrochlorothiazide, USP 50 mg

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

Store at 20° to 25°C (68° to 77°F).

**[See USP Controlled Room
Temperature.]**

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM0445A4

Each tablet contains:
Metoprolol tartrate, USP 100 mg
Hydrochlorothiazide, USP 50 mg

NDC 0378-0445-01

**Metoprolol
Tartrate and
Hydrochlorothiazide**
Tablets, USP

**100 mg/
50 mg**

Mylan®

Rx only 100 Tablets

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication
out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from moisture.
Usual Dosage: See accompanying
prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
Mylan.com

RM0445A4



GTIN XXXXXXXXXXXXX
S/N XXXXXXXXXXXX
EXP MM YYYY
LOT XXXXXXXX

METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE

metoprolol tartrate and hydrochlorothiazide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-0424
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name		Basis of Strength
METOPROLOL TARTRATE (UNII: W5S57Y3A5L) (METOPROLOL - UNII:GEB06NHM23)		METOPROLOL TARTRATE
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)		HYDROCHLOROTHIAZIDE
		Strength
		50 mg
		25 mg

Inactive Ingredients	
Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics			
Color	ORANGE (peach)	Score	2 pieces
Shape	ROUND	Size	10mm
Flavor		Imprint Code	M;424
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-0424-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/20/2004	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076792	08/20/2004	

METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE

metoprolol tartrate and hydrochlorothiazide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-0434
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name		Strength
METOPROLOL TARTRATE (UNII: W5S57Y3A5L) (METOPROLOL - UNII:GEB06NHM23)		METOPROLOL TARTRATE 100 mg
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)		HYDROCHLOROTHIAZIDE 25 mg

Inactive Ingredients	
Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics			
Color	ORANGE (peach)	Score	2 pieces
Shape	OVAL	Size	15mm
Flavor		Imprint Code	M;434
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-0434-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/20/2004	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076792	08/20/2004	

METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE

metoprolol tartrate and hydrochlorothiazide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-0445
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name		Strength
METOPROLOL TARTRATE (UNII: W5S57Y3A5L) (METOPROLOL - UNII:GEB06NHM23)		METOPROLOL TARTRATE 100 mg
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)		HYDROCHLOROTHIAZIDE 50 mg

Inactive Ingredients	
Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics			
Color	ORANGE (peach)	Score	2 pieces
Shape	OVAL (capsule-shaped)	Size	18mm
Flavor		Imprint Code	M;445
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-0445-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/20/2004	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076792	08/20/2004	

